New chemical entities developed by the pharmaceutical industry as potentially useful drugs undergo extensive preclinical evaluation followed by clinical trials to evaluate efficacy and safety in human subjects. In the United States, the Food and Drug Administration (FDA) is charged with evaluating requests from pharmaceutical sponsors for approval to market new drugs or to expand indications for marketed drugs. Some of these decisions are relatively straightforward. Thus, a new drug that shows clear efficacy and little actual or theoretical risk for serious adverse effects and that represents a significant addition to the therapeutic armamentarium does not present a major problem for FDA regulators. Conversely, approval will not be granted for a new drug the efficacy of which cannot be demonstrated, a drug with serious adverse effects that are not shared by alternative treatments, and a drug that does not add importantly to available treatment in at least some patients. In many cases, however, efficacy may not be so clear-cut, risks may be (or may appear to be) more than minimal, and the pharmaceutical sponsor and the FDA may differ in their evaluation of each of these issues. In such cases, the FDA through its Center for Drug Evaluation and Research (CDER) has since 1972 been able to call on panels of experts to provide advice. For cardiovascular drugs, this advice is offered by the Cardiovascular and Renal Drugs Advisory Committee (CRAC). The goal of this article is to summarize how the deliberations of this committee have affected not only individual new drug submissions but also more generally the way in which new drugs are developed and evaluated.

Advisory committees do not actually “decide” whether drugs should be approved; rather, they provide advice to the FDA, where the final decisions with regard to drug approval rest. The FDA is not obliged to accept recommendations made by its advisory panels. The topics addressed by the CRAC during the past 7 years are listed in the Table. In some cases, the FDA presents to the CRAC relatively noncontroversial issues, both for the information of CRAC members and to determine whether the committee agrees with the FDA that the issues are indeed straightforward. Often, advice is sought when issues are not clear, and the FDA has occasionally focused the discussion on aspects of the submission that posed a problem rather than on the whole submission. An interesting example is the panel meeting to discuss the calcium channel blocker mibebradil, which focused on a specific issue (QT prolongation) that the FDA believed might affect the risk–benefit balance for the drug. That mibebradil is a potent CYP3A4 and CYP2D6 inhibitor and had potential for many interactions (the issue that ultimately caused the drug to be withdrawn) was not the focus of that meeting because the issue was considered to be well understood.

At the end of the discussion, the panel is not asked simply to vote for or against approval. Rather, the discussion is often but not always followed by votes on a series of questions, a probe of panel members’ opinions on the points debated, and sometimes recommendations for or against approval in a range of patient groups. Thus, as the examples described below emphasize, the open discussion may affect regulatory decisions as much as formal votes.

Composition of the Panel and Conduct of the Meetings

FDA staff solicit advice from the cardiovascular and wider communities for suggestions about membership, with the goal of assembling a panel with a broad range of expertise, including clinical cardiology and its subspecialties (eg, heart failure, electrophysiology), trial design and execution, biostatistics, and clinical pharmacology. The panel includes representatives from industry (nonvoting) and from the public and is intended to be diverse, with representation of minorities, women, and various geographic regions of the country. Specific rules with regard to conflict of interest have been developed and may preclude a standing member of an advisory committee from participating in the discussion or from voting on a particular issue. These conflict-of-interest rules reflect not only interests related to the sponsor of the new drug under consideration but also the interests of sponsors of competing marketed products.

Topics for discussion at open advisory panel meetings are published weeks in advance in the Federal Register. The sponsor submits a briefing document, intended for panel members and the FDA, no later than 3 weeks before the meeting. The FDA provides a completed detailed review and often an overview of the issues to be discussed; FDA staff craft specific questions that they wish to have the panel discuss and, in most instances, vote on. The FDA...
# Issues Discussed at FDA Cardiorenal Advisory Committee 1997–2004

<table>
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<tr>
<th>Date</th>
<th>Drug</th>
<th>Major Issue Discussed</th>
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<td>1997</td>
<td>Aspirin</td>
<td>Labelling: reduction of cardiovascular outcome events in patients with angina, peripheral vascular disease</td>
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<td>1997</td>
<td>Hydralazine/isosorbide combination</td>
<td>Do results of V-HeFT I and II make combination appropriate for approval for heart failure? How many primary end points are appropriate?</td>
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<td>1997</td>
<td>Captopril</td>
<td>Is analysis of results of phase 3 trials sufficiently compelling to allow drug to be approved for heart failure? Is there a change in medication for heart failure an appropriate component of a primary end point?</td>
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<td>1997</td>
<td>Mibefradil</td>
<td>Risk of ECG abnormalities (QT prolongation) in a new antihypertensive/antianginal</td>
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<td>1997</td>
<td>Epifibatide</td>
<td>Adjunct antithrombotic therapy: Was evidence from a single trial (IMPACT II) sufficiently persuasive?</td>
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<td>1997</td>
<td>Fenoldopam</td>
<td>Clinical trials of this parenteral antihypertensive conducted in patients with sufficiently severe hypertension? Does drug have risks (eg, QT prolongation)?</td>
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<td>1997</td>
<td>Enoxaparin</td>
<td>Can data from a single trial (ESSENCE), with a composite end point that includes recurrent angina, as well as mortality, be sufficient for approval?</td>
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<td>1997</td>
<td>Ciloprodigl</td>
<td>Is evidence from a single, large, active, controlled trial sufficient for approval? With which labeling with respect to subsets (previous history of stroke, myocardial infarction, peripheral vascular disease)?</td>
</tr>
<tr>
<td>1997</td>
<td>Bivalirudin</td>
<td>Can data from large active-control trials that failed to meet primary superiority end point nevertheless be used to support drug approval in selected subsets?</td>
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<td>1997</td>
<td>Dofetilide</td>
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<td>1997</td>
<td>Nefiridil</td>
<td>Uncertainty over effective dose (if any), apparent inability to titrate; longer time to efficacy and time to resolution of effects than other heart failure drugs; concern over hypotension, bradycardia, and renal dysfunction</td>
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<td>1997</td>
<td>Sotalol</td>
<td>Risk (QT prolongation and torsade de pointes) vs benefit of maintaining sinus rhythm in patients with atrial fibrillation</td>
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<td>1997</td>
<td>Antiarrhythmic drugs</td>
<td>Use of implantable cardioverter-defibrillators in antiarrhythmic drug trials</td>
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<td>1997</td>
<td>Ib/IIa blockers</td>
<td>Appropriate qualifying disease; end points and their timing to evaluate efficacy and safety</td>
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<td>1997</td>
<td>Ramipril</td>
<td>Expand indications in view of HOPE trial; specific labeling for diabetes (not prespecified in trial) indicated?</td>
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<td>1997</td>
<td>Leprudin</td>
<td>Can results of multiple trials with different sizes, end point definitions, and designs be pooled? Can results of heparin as an active control in ACS be interpreted because regimens and reported efficacy vary?</td>
</tr>
<tr>
<td>1997</td>
<td>Antiarrhythmic drugs</td>
<td>Use of implantable cardioverter-defibrillators in antiarrhythmic drug trials</td>
</tr>
<tr>
<td>1997</td>
<td>Bosentan</td>
<td>Efficacy demonstrated in severely ill patients with PAH vs risk of hepatotoxicity</td>
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<td>1997</td>
<td>Amloptrol</td>
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<td>1997</td>
<td>Ibesartan for CHF added to ACE inhibitors</td>
<td>Benefit in CHF (mainly to hospitalization) in Val-HeFT study mainly resulting from patients not receiving ACE inhibitors</td>
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<tr>
<td>1997</td>
<td>Pravastatin/aspirin combination</td>
<td>Can combination be justified on basis of meta-analysis of previous trial data?</td>
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<tr>
<td>1997</td>
<td>Losartan for nephropathy in type 2 diabetes mellitus</td>
<td>Single trial with a small treatment effect; on creatinine doubling, ESRD with an effect (also on ESRD alone); modest statistical evidence in single trial; can results of ibesartan and losartan support each other?</td>
</tr>
<tr>
<td>1997</td>
<td>Candesartan</td>
<td>Can trial that showed a small (2 mm Hg) advantage in blood pressure reduction over losartan be used to claim candesartan is superior for blood pressure control?</td>
</tr>
<tr>
<td>1997</td>
<td>Omapatril</td>
<td>Balancing benefit of a highly effective new antihypertensive vs risk of a serious adverse reaction (angiogenesis)</td>
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<tr>
<td>1997</td>
<td>Pravastatin/aspirin combination</td>
<td>Continuation of 1/2002 discussions focusing on safety of stopping and restarting combination (eg, peripertaneously) and on appropriate dose combinations</td>
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<tr>
<td>1997</td>
<td>Alfuzosin and vardenafil</td>
<td>Does QT prolongation by these drugs (for erectile dysfunction and prostatic hypertrophy) constitute a cardiovascular risk?</td>
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<tr>
<td>1997</td>
<td>Aspirin for primary prevention</td>
<td>Do new large clinical trials justify expansion of labeling of aspirin to include primary prevention?</td>
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<tr>
<td>1997</td>
<td>Ranolazine</td>
<td>Balancing risks of QT prolongation and/or syncope vs benefits of a new antianginal</td>
</tr>
<tr>
<td>1997</td>
<td>Ximelagatan</td>
<td>Balancing risks of hepatotoxicity vs benefits of new antithrombotic</td>
</tr>
</tbody>
</table>

ESSENCE indicates Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events trial; HOPE, Heart Outcomes Prevention Evaluation study; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; and ESRD, end-stage renal disease.
Rare Adverse Effects

One common issue with which the FDA and the CRAC have grappled is how to assess risk–benefit balance with new drugs the pharmacological profile of which suggests a small risk of a serious adverse effect. Some adverse effects are direct extensions of the “expected” pharmacology; bleeding associated with fibrinolytic agents, low-molecular-weight heparins, or platelet IIb/IIIa receptor blockers is an example. In such cases, it is not the adverse effect itself that attracts discussion but rather its frequency and how it fits into an overall assessment of benefit versus risk. Other cases include adverse effects that are less predictable: angioedema (with the angiotensin-converting enzyme (ACE)/neutral endopeptidase inhibitor omapatrilat), hepatotoxicity (with the endothelin receptor blocker bosentan and the angiotensin receptor blocker tasosartan), or drug-induced QT prolongation with a risk of torsade de pointes (TdP). Both omapatrilat and tasosartan were not recommended for approval because of these risks and because alternative therapies were available. Bosentan, by contrast, was recommended for approval despite clear evidence of hepatotoxicity because it offered oral therapy to patients whose only previous treatments were parenteral. In addition, a postmarketing “risk management” program was discussed for bosentan.

QT Prolongation

Prolongation of the QT interval by some antiarrhythmic drugs is well recognized and indeed may be inseparable from the effectiveness of these agents. For QT-prolonging antiarrhythmics discussed by the CRAC (notably sotalol and dofetilide), this effect has been associated with a readily detectable risk of TdP. In these cases, this risk has been acceptable to both the FDA and the CRAC for 2 reasons: (1) The drugs are thought to provide important benefits to some patients, and (2) the risk can be “managed” in the sense that patients at especially high risk (eg, renal failure) can be identified and excluded, and monitoring procedures can be put in place to identify hyperresponders and therefore reduce risk.

The cardiorenal divisions of the CDER and thus the CRAC also have become involved in advising other divisions in evaluating the prolongation of the QT interval and associated potential risk for TdP by many “noncardiovascular” drugs. Although this risk has been recognized (eg, for antipsychotic drugs) for many years, the problem began to affect drug evaluation and development in the early 1990s with the recognition that drug interactions (causing inhibition of metabolism) could lead to marked accumulation in plasma of the antihistamine terfenadine; dozens of cases of TdP were reported to the FDA. This experience had at least 3 important consequences for drug development. First, new drug-evaluation packages now include a greater focus on drug interactions, active drug metabolites, clinical pharmacokinetics, and the likelihood of an unusual drug response if a specific pathway of drug metabolism is inhibited. Second, preclinical evaluation of most new drug entities now includes studies of their effects on cardiac ion currents, action potentials, or both. Third, early development programs now typically include an evaluation of the effect on QT interval at therapeutic and even supratherapeutic dosages of a new drug entity, often with a concomitant inhibition of drug metabolism. The FDA has published a draft international guidance document on this issue, and the question of how best to approach QT prolongation by nonantiarrhythmic drugs remains under active discussion in academic communities and regulatory agencies around the world.

Topics Addressed

Sponsors naturally put their best foot forward during an advisory panel meeting. Historically, general issues on which an FDA review has focused include appropriate use of statistics, clear definitions of efficacy and adverse effects, risk–benefit considerations in specific subgroups (eg, different ethnicities, both genders, older adults), clinical pharmacokinetics and the potential for drug interactions, and whether data gathered in one clinical trial setting can be used to predict how a drug might work in another. Recurring themes discussed by the CRAC at the request of the FDA include the following:

- Whether the proposed drug dose is the most appropriate one
- How to incorporate infrequent but serious potential risks into an overall risk–benefit consideration
- What special statistical considerations are made in the analysis of active control trials
- How to evaluate composite end points when different components of the end point contribute variably to outcome
- Whether data from a single trial can be sufficient for approval (the FDA, in general, has required 2 positive trials)
- Whether a meta-analysis can substitute for persuasive individual trials

Some meetings are devoted not to a specific new drug but rather to questions of broad interest to the FDA and the drug-development communities. The remainder of this article summarizes some recent discussions and how they have been important in changing thinking about how drugs should be evaluated before approval and how marketed drugs should be used.
When the potential dangers of QT prolongation by terfenadine and other drugs were recognized, a critical issue was whether there was an effect that was so small (eg, a few milliseconds) as to be inconsequential. CRAC discussions have recently involved antibiotics, antipsychotics, and drugs for urologic indications, and a consensus seems to be emerging that drugs producing only minor degrees of QT prolongation (eg, about 5 ms), with no risk of unusual pharmacokinetic responses or drug interactions, may carry little if any risk. Most recently, the CRAC evaluated ranolazine, a new antianginal agent that also prolongs QT intervals. Basic science data were presented to suggest that ranolazine may, like amiodarone, prolong QT interval without conferring an increased risk of TdP. Although the panel was receptive to this new science, it is not yet clear whether it will affect the ultimate evaluation of ranolazine or other drugs. Thus, attitudes about QT interval prolongation continue to evolve within the panel, the FDA, and the scientific community.

**End Points**

One contentious issue has been assessment of end points that were not specified as primary in a trial, when the specified primary end point failed. In general, the CRAC has agreed with cautious statistical arguments that accepting such unspecified end points would unacceptably increase the study’s “alpha error.” An exception that provides insights into the difficult nature of the questions the committee often faces was the consideration of carvedilol for postinfarction treatment of left ventricular dysfunction (based on the CARE trial). The Post infarction survIval versArinone (CAPRICORN) study. In this case, the committee recommended approval on the basis of an unspecified but statistically significant survival benefit (it had been specified but was changed midstudy) that was supported by a great deal of external data on β-blockers after infarction and the effect of carvedilol in heart failure.

The FDA, in general, has viewed a single positive trial with a P<0.05 as a relatively weak indicator of efficacy and has therefore expected >1 positive study for most new drugs. It has, however, accepted single studies that were statistically persuasive, especially for survival, for which conducting a second study would be ethically difficult. The positive inotropic agent vescarinone illustrates a reason for the 2-trial philosophy. An initial trial of vescarinone in heart failure involving 554 patients showed dramatically improved survival (with no change in symptoms) at 60 mg/d but increased mortality at 120 mg/d. The CRAC recommended against approval because there was only a single trial with an unusual reverse dose-response relationship and no symptom benefit at 60 mg/d. Subsequently, a larger trial (3833 patients) demonstrated increased mortality with 60 mg/d and a trend toward increased mortality even with 30 mg/d.

The discussion of the role of angiotensin receptor blockers for the preservation of renal function in type 2 diabetes mellitus with proteinuria presented another variation on the theme of small trials with borderline probability values. Irbesartan was evaluated principally in a 1700-patient trial comparing the effects of irbesartan, amlodipine, and placebo on a composite end point (first occurrence of mortality, end-stage renal disease, or doubling of serum creatinine). Although this primary end point was met (P=0.023), the result was driven by the effect on creatinine elevation only, rather than on progression to end-stage renal disease. In addition, because the probability value was borderline, there was discussion of how the result might have been influenced by the handling of data from small patient groups (eg, those randomized who never received the drug). The committee was divided, and 3 months later it considered data from a trial of 1513 patients that compared losartan with placebo with a similar primary end point (first occurrence of death, end-stage renal disease, or doubling serum creatinine). This trial also met its primary end point with a modest probability value (P=0.022), and the questions asked of the committee were nearly the same as those for irbesartan: sensitivity of a borderline probability value to handling specific patient subsets (dropouts, in this case) and that the positive outcome was driven largely by the creatinine-doubling end point. The committee’s discussion at the second meeting included consideration of both the irbesartan and the losartan data. They found that the single studies of related drugs supported each other and that the described beneficial effects of captopril in patients with type 1 diabetes mellitus were also pertinent; approval was recommended.

Even 2 incontrovertibly positive trials can raise important issues in ability to approve. The IMPACT-II (Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis) trial showed a positive effect of the platelet IIb/IIIa receptor blocker epifibatide at low doses as adjunctive therapy in patients undergoing percutaneous transluminal coronary angioplasty. The primary end point assessed at 30 days was death, acute myocardial infarction, or a need for reintervention. In part because this was a single trial, the CRAC voted against recommending approval. The panel later reconsidered the drug in light of the results of a second trial (PURSUIT; Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) that studied almost 10 000 patients with acute coronary syndrome (ACS) at higher dosages; PURSUIT was not discussed at the first meeting because the results were not yet available. The primary end point was death or myocardial infarction by 30 days, for which the trial showed a P=0.001; however, this result was driven almost exclusively by a reduction in myocardial infarction (7.8 versus 6.2%, P=0.002), with no change in mortality (3.7 versus 3.5%, P=0.531). The question was then whether the 2 trials, performed in different patient populations at different doses with different end points, could nonetheless be considered as supporting each other and be a basis for recommending approval, and if so, for which indication at which dose; the vote in this case was for approval.

Another variation on the problem of combining studies with different designs and outcomes arose during deliberations over the initial submission of data to support use of carvedilol in heart failure. At an initial meeting, data from 4 relatively small placebo-controlled trials with composite end points were discussed. Some of the trials failed to reach their primary end point (eg, exercise test improvement), and in the case of composite end points, statistical significance was
driven by 1 end point component (eg, change in heart failure medication) that seemed less persuasive than others (eg, hospitalization, death). When the data from the 4 trials were combined, however, the drug strikingly reduced mortality, although there were few events and this analysis was not prespecified. The CRAC initially recommended that carvedilol not be approved for heart failure, but at a subsequent meeting the panel recommended approval when a second trial met its prespecified end point.

Deliberations over the angiotensin receptor blocker valsartan in heart failure illustrate the issues involved in considering subset analysis in a single large trial. Valsartan Heart Failure Trial (Valsartan Heart Failure Trial), involving 5010 patients, compared valsartan with placebo in patients already treated with ACE inhibitors and β-blockers, who continued their treatment. This background therapy was not mandated, however, and 366 patients (7.3%) did not receive an ACE inhibitor. Although valsartan was superior to placebo (P=0.009) for a composite end point of mortality + congestive heart failure (CHF) hospitalization + resuscitation + change in CHF therapy, this positive outcome was driven almost exclusively by CHF hospitalizations and by the 7.3% of patients not taking ACE inhibitors. Not only was there no significant effect in the 93% taking ACE inhibitors, what beneficial effect there was in this group occurred primarily in patients taking less than the recommended doses. Patients taking both an ACE inhibitor and a β-blocker who were given valsartan actually did significantly worse than did patients given a placebo. Thus, many of the questions to the CRAC centered around which populations if any valsartan might be considered for approval in heart failure. Because of its striking beneficial effect in the group not taking ACE inhibitors, valsartan is now approved for heart failure in patients who are intolerant of ACE inhibitors.

**Active Control Trials**

In many cases, it is possible to mount studies comparing a new drug with a placebo, and these studies are readily interpreted. Where there are therapies that are proven to be effective for a life-threatening condition, however, it is unethical to withhold standard therapy. In such cases, new drugs can be compared either with placebo as add-on therapy to “standard” background treatment or with active controls. As more and more therapies are shown to be effective in large populations, the issues involved in conducting and interpreting these trials have become more common in cardiovascular medicine.

“Add-on” studies are statistically rigorous and readily interpreted but give no information on use of the drug alone. Active control trials present a special set of problems in design, execution, and interpretation. For example, for a new drug to be approved, it should be demonstrably superior to placebo. In an active control trial, there is no placebo and the control agent is chosen because its effect versus placebo is thought to be well described. An active control trial, therefore, is designed to show that the new drug is not worse than the control by an amount greater than the effect of the control drug versus placebo (the “noninferiority margin”). Hence, analysis of the results of an active control trial must provide assurance that the control drug really had its expected effect in the study and should describe confidence intervals around this control effect, which is often difficult to specify. Furthermore, whereas rigorous adherence to the protocol maximizes the likelihood of finding a true difference between drug and control in a placebo-controlled trial, sloppy conduct of an active control trial maximizes the likelihood of finding no difference—the sought-after result.

A detailed consideration of active control trials took place in the CRAC’s discussion of CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events), a trial of >19 000 patients with coronary disease, cerebrovascular disease, or peripheral vascular disease that compared clopidogrel with the active control aspirin, the effects of which against placebo were believed to be well defined. In this case, clopidogrel was nominally superior (P=0.05) to aspirin, producing an 8% reduction in a composite primary end point, a persuasive argument for at least equivalence. Despite the large number of patients and the attainment of statistical significance, several issues nevertheless emerged during the discussion: Could the sponsor claim that clopidogrel was superior to aspirin? The consensus was no. Could individual subsets of patients (eg, those entering the trial with myocardial infarction versus those entering the trial with peripheral vascular disease) be delineated to make a clear claim for superiority of one therapy over the other? Despite the large size of the trial, there was no plan for such analysis, so the consensus was no.

Studies of low-molecular-weight heparins versus standard heparin for ACS faced a variation on this issue because although heparin was viewed as a standard therapy, its efficacy had not been examined in controlled trials and the dose at which efficacy may be achieved in ACS was not well defined.

**The Future**

It is the mandate of the FDA and other regulatory agencies worldwide to maintain a balance between the timely approval of new and effective therapies and the need to protect the public from harmful drugs. As this discussion has highlighted, evaluating the safety and efficacy of new drugs is often fraught with obvious and not-so-obvious pitfalls. These evaluations require wide-ranging expertise not only in the conduct and interpretation of clinical trials but also in new areas of basic and clinical science such as the molecular pharmacology of drug metabolism and elimination, ion channel biology, platelet and vascular function, and genomics. The solicitation of expert advice and open discussion by the CRAC and other advisory panels thus constitutes an important component of the drug evaluation process.

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References

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